(54) Title: PROCESS FOR PREPARING 3-(SUBSTITUTED PHENYL)-5-THIENYL OR FURYL)-1,2,4-TRIAZOLES AND NOVEL INTERMEDIATES UTILIZED THEREIN

(57) Abstract

New synthetic procedures for preparing insecticidal 3-(substituted phenyl)-5-(thienyl or furyl)-1,2,4-triazoles utilizing thioimidate intermediate.

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PROCESS FOR PREPARING 3-(SUBSTITUTED PHENYL)-5-THIENYL OR FURYL)-1,2,4-TRIAZOLES AND NOVEL INTERMEDIATES UTILIZED THEREIN

5   This invention provides new synthetic procedures and intermediates for preparing insecticidal 3-(substituted phenyl)-5-thienyl or furyl)-1,2,4-triazoles.

WO 98/47894 discloses a series of highly active new insecticides. Although that patent application discloses
10   suitable laboratory methods for preparation of the compounds, a need exists for a commercially applicable manufacturing process.

The present invention provides a process for preparing compounds of the formula (1)

15

wherein

Ar is substituted phenyl;

Y is O or S;

R^3 is selected from H, halo, lower alkyl, (C_7-C_{21})
20   straight or branched chain alkyl, hydroxy, lower alkoxy, haloalkyl, haloalkoxy, alkoxyalkyl, alkoxyalkoxy, lower alkenyl, lower alkynyl, haloalkenyl, CN, NO_2, COR^6, CO_2R^6, $CON(R^6)_2$, (C_3-C_6) cycloalkyl, $S(O)_mR^6$, $-OSO_2R^6$, SCN, $-$
$(CH_2)_nR^6$, $-CH=CHR^6$, $-C{\equiv}CR^6$, $-(CH_2)_qOR^6$, $-(CH_2)_qSR^6$, $-$
25   $(CH_2)_qNR^6R^6$, $-O(CH_2)_qR^6$, $-S(CH_2)_qR^6$, $-NR^6(CH_2)_qR^6$,

$$-NR^6 \overset{O}{\underset{}{\parallel}} N(R^6) , \quad \overset{N^{\nearrow OR^6}}{\underset{}{\parallel}} R^6 , \quad -O \overset{O}{\underset{}{\parallel}} R^6 , \text{ or } -S \overset{O}{\underset{}{\parallel}} R^6 ,$$ pyridyl,

substituted pyridyl, isoxazolyl, substituted isoxazolyl, naphthyl, substituted naphthyl, phenyl, substituted phenyl, thienyl, substituted thienyl, pyrimidyl,

5   substituted pyrimidyl, pyrazolyl, or substituted pyrazolyl;

R^4 and R^5 are independently H, halo, lower alkyl, lower alkoxy, haloalkyl, haloalkoxy, CN, CO_2R^6, $CON(R^6)_2$, or $S(O)_m$ alkyl, or

10   if R^4 and R^5 are attached to adjacent carbon atoms, they may join to form a 5 or 6 member saturated or unsaturated carbocyclic ring which may be substituted by 1 or 2 halo, lower alkyl, lower alkoxy or haloalkyl groups;

15   R^6 is H, lower alkyl, haloalkyl, lower alkenyl, lower alkynyl, phenyl, or substituted phenyl;

m is 0, 1, or 2;

n is 1 or 2;

p is an integer from 2 to 6; and

20   q is 0 or 1;

which comprises the steps of:

(a)   reacting a compound of formula (2)

$$\text{Ar}-\overset{S-R^7}{\underset{NH}{\overset{\displaystyle \|}{C}}} \quad (2)$$
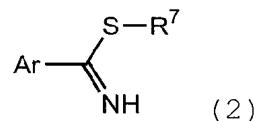
wherein Ar is as defined in formula (1) and R^7 is lower

25   alkyl, or an acid addition salt thereof, with an acid chloride of the formula (3)

$$\underset{\text{Cl}}{\overset{\text{O}}{\underset{||}{\text{C}}}}\text{(3)}$$
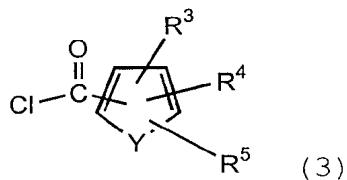
wherein Y, R^3, R^4, and R^5 are as defined in formula (1), in an inert organic solvent the presence of an organic or inorganic base to produce the adduct-intermediate of formula (4)

$$\text{(4)}$$
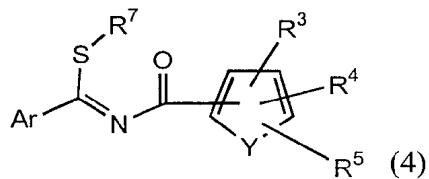
wherein Ar, Y, R^3, R^4, and R^5 are as defined in formula (1) and R^7 is lower alkyl; and

(b) optionally isolating said adduct intermediate, and

(c) reacting said adduct-intermediate with methyl hydrazine to produce the compound of formula (1).

Adduct-intermediates of formula (4) are novel compounds, and they are an important aspect of the invention.

Adduct-intermediates that are preferred based on desirable properties of the final products they may be used to produce are those of formula
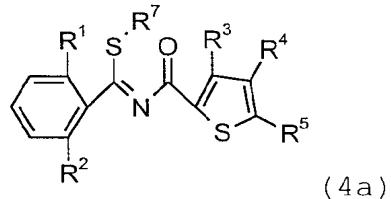
$$\text{(4a)}$$

wherein

R^1 and R^2 are independently F or Cl;

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R^3, R^4, and R^5 are independently H, CH_3, Cl or Br; and

R^7 is lower alkyl.

Most preferred adduct intermediates are those of

5   formula (4a) wherein R^1 is Cl, R^2 is F, R^7 is CH_3, and:

(a) R^3, R^4, and R^5 are each Cl;

(b) R^3 and R^4 are each Br and R^5 is H; or

(c) R^3 is CH_3, R^4 is Cl or Br, and R^5 is H.

In another of its aspects, the invention provides

10   the methyl sulfate salt of a compound of the formula

(2a)
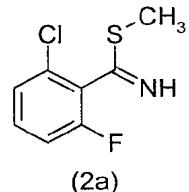
Throughout this document, all temperatures are given in degrees Celsius, and all percentages are weight percentages unless otherwise stated.

15   The term "lower alkyl" refers to (C_1-C_6) straight hydrocarbon chains and (C_3-C_6) branched and cyclic hydrocarbon groups.

The terms "lower alkenyl" and "lower alkynyl" refer to (C_2-C_6) straight hydrocarbon chains and (C_3-C_6)

20   branched hydrocarbon groups containing at least one double or triple bond, respectively.

The term "lower alkoxy" refers to -O-lower alkyl.

The terms "halomethyl" and "haloalkyl" refer to methoxy and lower alkyl groups substituted with one or

25   more halo atoms.

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The terms "halomethoxy" and "haloalkoxy" refer to methyl and lower alkoxy groups substituted with one or more halo atoms.

The term "alkoxyalkyl" refers to a lower alkyl group substituted with a lower alkoxy group.

The terms "substituted naphthyl", "substituted thienyl," "substituted pyrimidyl," "substituted pyrazolyl," "substituted pyridyl," and "substituted isoxaxolyl" refer to the ring system substituted with one or more groups independently selected from halo, halo (C_1-C_4) alkyl, CN, NO_2, (C_1-C_4) alkyl, (C_3-C_4) branched alkyl, phenyl, (C_1-C_4) alkoxy, or halo (C_1-C_4) alkoxy.

The term "substituted phenyl" refers to a phenyl group substituted with one or more groups independently selected from halo, (C_1-C_{10}) alkyl, branched (C_3-C_6) alkyl, halo (C_1-C_7) alkyl, hydroxy (C_1-C_7) alkyl, (C_1-C_7) alkoxy, halo (C_1-C_7) alkoxy, phenoxy, phenyl, NO_2, OH, CN, (C_1-C_4) alkanoyl, benzoyl, (C_1-C_4) alkanoyloxy, (C_1-C_4) alkoxycarbonyl, phenoxycarbonyl, or benzoyloxy.

The term "substituted benzenesulfonyl" refers to p-chlorobenzenesulfonyl and p-toluenesulfonyl.

Unless otherwise indicated, when it is stated that a group may be substituted with one or more substituents selected from an identified class, it is intended that the substituents may be independently selected from the class.

Alkyl benzthioimidates of formula (2) are known in the literature. They are preferably used in the present invention as an acid addition salt. For example, tetrafluoroboric acid, hydrogen chloride, hydrogen bromide, hydrogen iodide, or the like, may be used. The methyl sulfate salt is preferred.

Thioimidates are readily available through alkylation of the corresponding thioamides which are themselves commercially available or can be made from the amide (Phosphorus Sulfur (1985), 25(3), 297-305) or

5   nitrile (Chem.-Ztg. (1980), 104(12), 365-7; J. Chem. Soc. (1952), 742; Can. J. Chem. (1985), 63, 3075).

Reaction of the acid chloride (3) and the imidate (2) to give the adduct (4) can generally be accomplished in any inert solvent with any organic or inorganic base.

10   Reaction of compounds of formula (4) with methyl hydrazine gives the desired triazoles, generally in good yield and with a high degree of regiospecificity. An example of a previous application of a similar process is given in Synthesis, 483 (1983). In regard to

15   regiospecificity, the undesired possible coproducts are the 5-(substituted phenyl)-3-thienyl or furyl isomers of the desired 3-(substituted phenyl)-5-thienyl or furyl-1,2,4-triazoles.

Compounds of formula (1) can also be made starting

20   with an alkyl benzimidate, as illustrated in the following comparative example. It has been found, however, that the process of the invention, utilizing alkyl benzthioimidates, provides significantly better yields.

25   Comparative Example 1
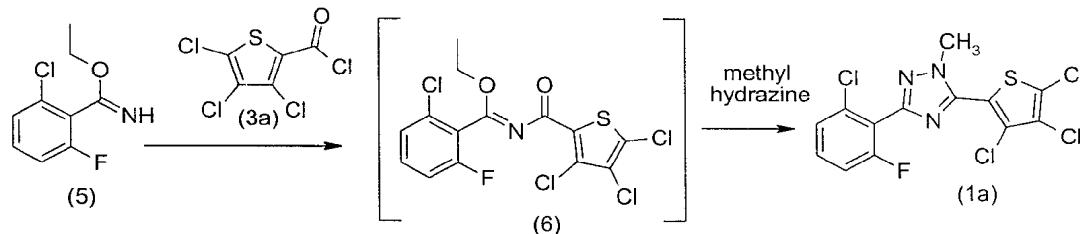
Briefly, the reaction of ethyl 2-fluoro-6-chlorobenzimidate (5) with 3,4,5-trichloro-2-thienoyl chloride (3a) was performed in toluene using

triethylamine as an acid scavenger. The presumed
intermediate (**6**) which was not isolated, then reacted
with methyl hydrazine 3 hr at reflux to give 1-methyl-3-
(2-chloro-6-fluoro)phenyl-5-(3,4,5-trichloro-2-thienyl)-
5   1H-1,2,4-triazole (**1a**) in 35% yield. The following
paragraphs describe each step of the synthesis in greater
detail.

A.   2-chloro-6-fluorobenzamide

The procedure of R. Balicki and L. Kaczmarek, Syn. Comm.,
10   **23**, 3149 (1993)was used. Into a 1 L round bottom flask
equipped with a magnetic stirrer was added acetone (60
mL), water (60 mL) , 2-chloro-6-fluorobenzonitrile (14.5
g, 93.5 mmol), urea (22.5 g, 374 mmol), 30% hydrogen
peroxide (42.4 g, 374 mmol), and potassium carbonate (1.3
15   g, 9.0 mmol). The resulting slurry was stirred at room
temperature overnight. Additional portions of urea (11.2
g, 30% hydrogen peroxide (41 g), acetone (30 mL) and
potassium carbonate (0.63 g) were added and the mixture
was allowed to stir for an additional 2 hr. Additional
20   portions of urea (11.2 g, 30% hydrogen peroxide (41 g),
acetone (30 mL) and potassium carbonate (0.63 g) were
again added and the mixture was allowed to stir
overnight. The acetone was removed in vacuo, the residue
extracted with methylene chloride, the organics were
25   combined, washed with brine, dried ($MgSO_4$) and the solvent
removed in vacuo to give 15.8 g (97.5% yield) of 2-
chloro-6-fluorobenzamide (97% pure by GC): mp140-141 °C;
1H NMR (CDCl3) d 7.2-7.4 (m, 2H), 7.0 (m, 1H), 6.3 (s, b,
1H), 5.9 (s, b, 1H).

30   B.   Ethyl 2-chloro-6-fluorobenzimidate (**5**)

Into a 1 L round bottom flask equipped with a mechanical
stirrer, thermometer, condenser, dropping funnel, under an
atmosphere of nitrogen was added methylene chloride (240
mL) and 2-chloro-6-fluorobenzamide (8.65 g, 50 mmol). The

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temperature of the mixture was cooled to approximately 0
°C and a solution of triethyloxonium tetrafluoroborate (55
mL of 1M soln) was added dropwise at a rate such that the
temperature did not rise over 0 °C. The resulting mixture
5   was allowed to warm to stir cold for 1 hr , the cooling
bath was removed, the mixture was allowed to warm to RT,
and was stirred at that temperature overnight. Due to
incomplete conversion the mixture was cooled to °5 C and
dropwise was added and additional 11 mL of 1M soln of
10   triethyloxonium tetrafluoroborate. The cooling bath was
removed and the mixture allowed to stir for an additional
24 hr. The mixture was cooled to 0 °C and an additional
portion of triethyloxonium tetrafluoroborate (10 mL) was
added dropwise, the bath removed and the mixture stirred
15   at RT for 19 hr. The temperature was lowered to 0 °C and
a solution of potassium carbonate (50%) was added
dropwise. After stirring for 15 min the layers were
separated, the aqueous layer washed with methylene
chloride, the organics combined, dried (Na$_2$SO$_4$), and the
20   solvent removed _in vacuo_ to give an oil: ethyl 2-chloro-6-
fluorobenzimidate (94%), starting material (5%). This
material was used without further purification.

C.   Preparation of 1-methyl-3-(2-chloro-6-fluoro)phenyl-5-
(3,4,5-trichloro-2-thienyl)-1H-1,2,4-triazole(**1a**) from ethyl
25   2-chloro-6-fluorobenzimidate (**5**)
Into 50 mL one necked round bottom flask equipped with a
magnetic stirrer and condenser under an atmosphere of
nitrogen was added 3,4,5-trichloro-2-thienyl carboxylic
acid (0.69 g, 3 mmol), EDC (20 mL), thionyl chloride
30   (0.53 g, 0.32 mL, 4.5 mmol) and several drops of DMF.
The mixture was allowed to reflux for 3 hr and the
solvent was removed _in vacuo_ to a constant weight. To a
three necked flask equipped with a condenser and
containing ethyl 2-chloro-6-fluorobenzimidate (94% pure,
35   0.60 g, 3.0 mmol), and triethylamine (0.10 g, 0.14 mL,

6.0 mmol), and toluene (10 mL) was added dropwise 3,4,5-
trichloro-2-thienoyl chloride dissolved in toluene (10
mL). The temperature of the mixture was brought to the
point of reflux and maintained at that temperature for 3

5   hr. To the refluxing mixture was added methyl hydrazine
(0.86 g, 1.0 mL, 9 mmol) dissolved in toluene was added
dropwise. The mixture was allowed to reflux for 1 hr.
The toluene was removed in vacuo and the residue was
purified via column chromatography to give 1-methyl-3-(2-

10   chloro-6-fluoro)phenyl-5-(3,4,5-trichloro-2-thienyl)-1H-
1,2,4-triazole (**1a**): 0.42 g (35% yield), GC[Mez80] at
19.1 min, mass 395/397/399.

<p align="center">Example 1</p>
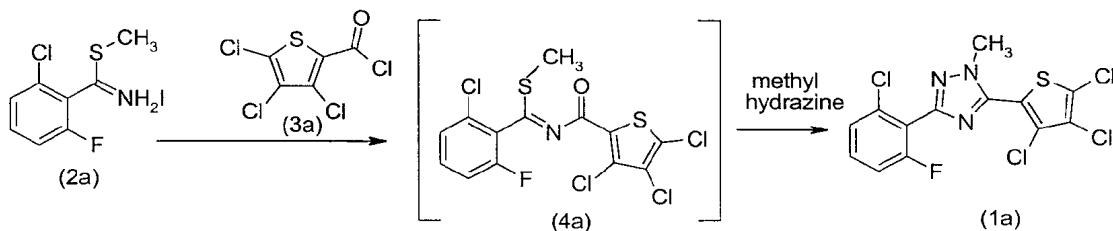
15   Briefly, the reaction of methyl 2-fluoro-6-
chlorobenzthioimidate hydroiodide (**2a**) with 3,4,5-
trichloro-2-thienoyl chloride (**3a**) was performed in
toluene using triethylamine as an acid scavenger. The
presumed intermediate (**4a**) which was not isolated, then

20   reacted with methyl hydrazine for 3 hr at reflux to give
1-methyl-3-(2-chloro-6-fluoro)phenyl-5-(3,4,5-trichloro-
2-thienyl)-1H-1,2,4-triazole(**1a**) in 78% yield.

The following paragraphs describe each step of the
synthesis in greater detail.

25   A.   Preparation of 2-chloro-6-fluorobenzthioamide

Into a 250-mL three necked round bottom flask equipped
with a mechanical stirrer, dry ice condenser, dropping
funnel, and outlet to a trap filled with bleach was added
pyridine (45 mL), 2-chloro-6-fluorobenzonitrile (15.5 g,

0.1 mol), triethylamine (13.4 g, 18.6 mL, 0.133 mol), and sodium sulfide hydrate (36.0 g, 0.15 mol). The temperature of the resulting solution was lowered to approximately 5 °C using an ice bath. To the stirred

5   slurry was added dropwise concentrated hydrochloric acid (25.8 g, 0.266 mol). The rate of addition of the hydrochloric acid was such that the temperature of the reaction mixture did not exceed 25 °C with an addition time of 20 min. The cooling bath was removed and the

10 slurry was allowed to warm to RT and to stir over night. An additional 40 grams of sodium sulfide and 50 mL of hydrochloric acid was added to the mixture and allowed to stir over night. An additional 40 grams of sodium sulfide and 50 mL of hydrochloric acid was added and the

15 mixture allowed to stir over the weekend. The mixture was poured into water (2 L) and was extracted with ether. The ether layer was washed with dilute sulfuric acid, water, brine, dried (MgSO$_4$), and the solvent removed in vacuo to give 16.1 g of crude product which was

20 recrystallized from ethyl acetate to give 2-chloro-6-fluoro-benzthioamide as light yellow crystals: mp 156-158 °C.

B.   Preparation of methyl 2-chloro-6-fluorobenzthioimidate hydroiodide (**2a**)

25 Into a 50 mL three necked round bottom flask equipped with a magnetic stirrer was added 2-chloro-6-fluorobenzthioamide (3.78 g, 20 mmol) and acetone (20 mL). Dropwise was added iodomethane (2.84 g, 1.24 mL, 20 mmol) and the mixture was allowed to stir at room

30 temperature overnight with monitoring via HPCL (60/40 acetonitrile/water). The solids were removed via filtration and washed with small portions of acetone to give methyl 2-chloro-6-fluorobenzthioimidate hydroiodide as a light yellow solid: 3.1 g (46.9% yield): ^{1}H NMR

35 (DMSO-d$_6$) δ 7.7 (m, 1H), 7.5 (m, 2H), 2.7 (s, 3H).

C.   Preparation of 1-methyl-3-(2-chloro-6-fluoro)phenyl-5-
(3,4,5-trichloro-2-thienyl)-1H-1,2,4-triazole (**1a**) from 2-
chloro-6-fluorobenzthioimidate hydroiodide (**2a**)

Into 50 mL one necked round bottom flask equipped with a

5   magnetic stirrer and condenser under an atmosphere of

nitrogen was added 3,4,5-trichloro-2-thienyl carboxylic

acid (0.69 g, 3 mmol), EDC (20 mL), thionyl chloride

(0.53 g, 0.32 mL, 4.5 mmol) and several drops of DMF.

The mixture was allowed to reflux for 3 hr and the

10   solvent was removed _in vacuo_ to a constant weight. To a

three necked flask equipped with a condenser and

containing methyl 2-chloro-6-fluorobenzthioimidate

hydroiodide (0.99 g, 3.0 mmol), and triethylamine (0.20

g, 0.28 mL, 12 mmol), and toluene (20 mL) was added

15   dropwise 3,4,5-trichloro-2-thienoyl chloride dissolved in

toluene (10 mL). The mixture was brought to the point of

reflux and maintained at that temperature for 3 hr. To

the refluxing mixture was added methyl hydrazine (0.86 g,

1.0 mL, 18 mmol) dissolved in toluene was added dropwise.

20   The mixture was allowed to reflux for 1 hr, the toluene

was removed _in vacuo,_ and the residue chromatographed on

silica gel to give 0.87 g (73% yield), GC[Mez80] at 19.1

min, mass 395/397/399.

        Thus, the process of the invention provided a

25   significantly better yield (73% versus 35%)than the

process using an alkyl benzimidate in place of the alkyl

benzthioimidate required by the invention.

        The preferred process for preparing the methyl

2-chloro-6-fluorobenzthioimidate produces the methyl

30   sulfate salt.

Example 2

Preparation of methyl 2-chloro-6-fluorobenzthioimidate
using dimethylsulfate
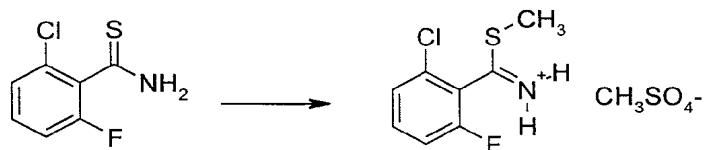
Into a 25-mL three-necked round bottom flask equipped
with a magnetic stirrer was added 2-chloro-6-
fluorobenzthioamide (1.89 g, 10.0 mmol) and toluene (10

5   mL). Dimethylsulfate was added dropwise and the mixture
was allowed to stir at reflux using a Dean Stark trap.
The solids were removed via filtration and washed with
small portions of toluene to give methyl 2-chloro-6-
fluorobenzthioimidate as a light yellow solid: 2.7 g

10   (87% yield): ^{1}H NMR (DMSO-d$_6$) δ 7.7 (m, 1H), 7.5 (m, 2H),
3.3 (s, 3H), 2.7 (s, 3H); 98% pure by HPLC analysis.

        Comparing the results of Example 2 with those
of Example 1C, it is clear that Example 2 is a
significant improvement. Example 2 is higher yielding

15   (87% versus 46%), yields a purer product (98% versus 96%)
and uses a reagent, dimethyl sulfate, that is much
cheaper both in terms of initial cost and disposal
issues.

        The following example illustrates the complete

20   process incorporating use of the methyl sulfate salt and
isolation of the adduct intermediate.

                        Example 3

A.   2-Chloro-6-Fluorobenzthioamide

2-Chloro-6-fluorobenzonitrile, (99.1%, 62.2 g, 0.40 mol)

25   was weighed into a 1-L three-necked roundbottom flask
equipped with a condenser and an overhead electric
stirrer, along with Et$_3$N (78 mL, 56.6 g, 0.56 mol) and 180
mL (176.04 g, 2.23 mol) of pyridine. The reactor was
purged with a slow stream of N$_2$ and vented to a 13% bleach

30   solution. The stirring solution was cooled to −19°C in a
CCl$_4$/dry ice bath, and H$_2$S gas (33.6 g, 0.99 mol) was

                            -12-

sparged below the liquid surface at a rate of 0.4 g/min over a period of 82 min. During the gas addition, the solution temperature rose to -11°C. The yellow-green solution was allowed to gradually warm to 25°C and stir

5 overnight with a slow N_2 purge of the reactor head space into bleach solution. The solution was poured into 1.6 L of ice water, stirred, and the resulting white crystals were collected on a buchner funnel and rinsed with additional water. After 2 h of air drying, the moist

10 filter cake was vacuum oven dried for 5 h at 65°C to give 54.5 g of 2-Chloro-6-Fluorobenzthioamide (72% wt. % yield), mp 155-160°C, having a GC area % purity of 98.8 % and containing 1.2 % 2-Chloro-6-fluorobenzonitrile.

B. Methyl 2-chloro-6-fluorobenzthioimidate methyl

15 sulfate salt

2-Chloro-6-fluorobenzthioamide (21.9 g, 0.12 mol) and dimethyl sulfate (12 mL, 16.0 g, 0.13 mol) were stirred together in 100 mL of toluene and refluxed for 2 h. The slurry was cooled to 25°C and the white crystals

20 collected on a glass buchner funnel and rinsed with a small quantity of acetone. After air suction drying for 1 h, 35.5 g of methyl 2-chloro-6-fluorobenzthioimidate methylsulfate salt was obtained, mp 147-151°C, representing a nominal wt. % yield of 96%.

25 A sample of this salt was recrystallized from cold isopropanol followed by vacuum oven drying at 75°C to give white crystals, mp 152-157°C. Elemental analysis results are summarized in the table below.

	Theoretical	Found
C	34.23%	34.47%
H	3.51%	3.61%
N	4.44%	4.45%

| Cl | 11.23% | 11.27% |
| S | 20.31% | 20.16% |

C.   Methyl-2-chloro-6-fluoro-N-[(3,4,5-trichloro-2-thiophene)carbonyl]-benzenecarboximidothioate.
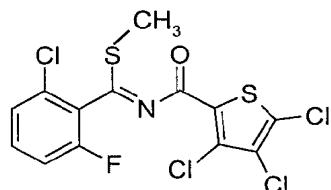
2-Chloro-6-fluorobenzthioimidate methylsulfate salt (35.5
g, 0.11 mol) and 155 mL of toluene were placed into a 1 L
three-necked roundbottom flask with a bottom drain and
overhead stirrer. The solution was cooled with an ice
bath, and to this slurry was added triethylamine (32 mL,
23.2 g, 0.23 mol). A mild exotherm was noted. A
solution of 3,4,5-trichloro-2-thiophenecarbonyl chloride
(30.69 g, 0.12 mol) was added dropwise over 30 min at
0°C. After 1 h of cooling, the ice bath was removed and
the mixture was stirred at 25°C for 3 days. The solution
was washed with two 250 mL portions of water, and the
toluene was evaporated to give 41.3 g of tan solid. This
solid was washed with CH_3CN, filtered and dried to give
32.8 g of white solid, m.p. 124-126°C, for a weight %
yield of 70.2 %.

A purified sample of the adduct was obtained by
recrystallization from warm CH_3CN followed by vacuum oven
drying at 60°C for 3 h; m.p. 125-128°C. Elemental
analysis results are summarized in the table below.

	Theoretical	Found
C	37.43 %	37.18 %
H	1.45 %	1.43 %
N	3.36 %	3.62 %
Cl	34.00 %	34.08 %
F	4.55 %	5.30 %
S	15.37 %	15.64 %

D.   1-Methyl-3-(2-chloro-6-fluoro)phenyl-5-(3,4,5-trichloro-2-thienyl)-1H-1,2,4-triazole.

The adduct intermediate of part C (6.1 g, 0.0146 mol) and 75 mL toluene were placed into a 250 mL three-necked

5   flask and brought to reflux. Methylhydrazine (1.6 mL, 1.39 g, 0.0301 mol) as a solution in 25 mL of toluene was added dropwise to the refluxing solution over a period of 1 h. The solution was refluxed for an additional 2 h, then was cooled to 25°C, washed with aqueous Na_2CO_3, then

10   water, and the organic phase was evaporated to give a viscous oily residue. The ratio of regio isomers by GC area % analysis was 13.7/1 in favor of the desired isomer. The oily residue was triturated with a small volume of CH_3CN, cooled to 0°C in a freezer for 1 h, and

15   the resulting white crystals were collected on a buchner funnel and air-suction dried to give 4.1 g (70%) of the desired product, m.p. 128-130.5°C, with a GC area % purity of 98.3 % and containing 1.4 % of a regio isomer impurity.

20   A preferred synthetic method is illustrated in the following Scheme I:
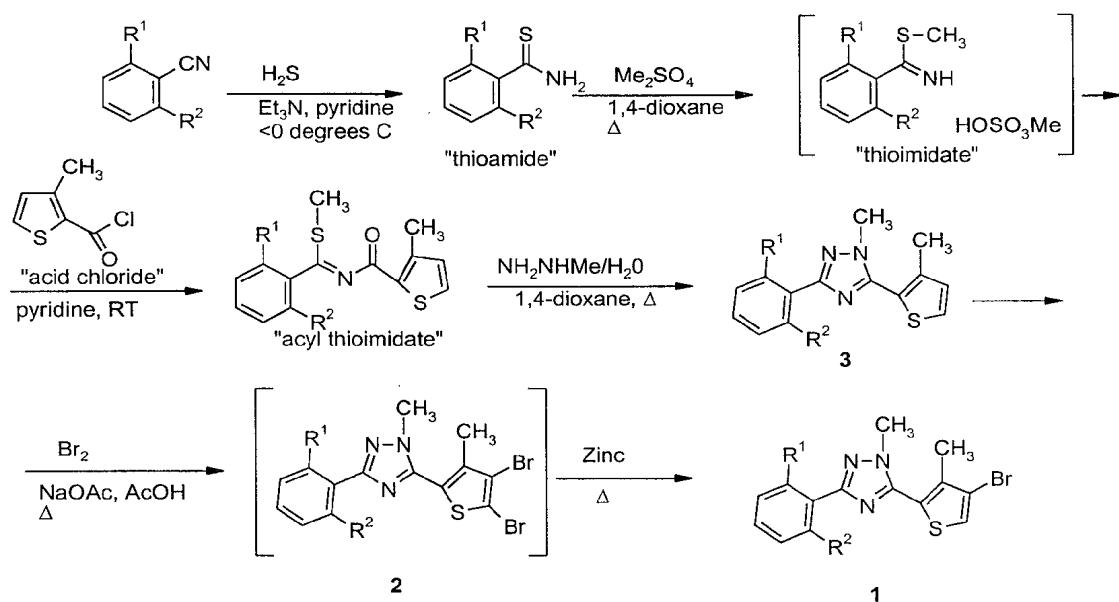
The first step of this process involves preparation of
the thioamide starting material. The thioamide was
converted to the thioimidate using dimethyl sulfate in

5   1,4-dioxane. Any known imidate forming procedure known
in the literature can be used for this transformation.
Common methylating agents such as methyliodide,
methylbromide and dimethyl sulfate can be used. Any
common solvent compatible with the reaction conditions

10 can be used, with toluene, acetonitrile, 1,4-dioxane,
THF, and 1,2-dichloroethane most convenient. Reaction
temperatures range from RT to the reflux temperature of
the solvent. The thioimidate can be isolated as its salt
or used directly without isolation in the next

15 transformation.

The thioimidate was next acylated with 3-methyl-2-
thiophenecarbonyl chloride ("acid chloride") to give the
acyl thioimidate adduct. Any known acylation conditions
can be used for this transformation. Any common organic

20 and inorganic base can be used, with Na_2CO_3, $NaHCO_3$,
pyridine and triethylamine most convenient. Solvents
preferred include 1,4-dioxane, THF, dichloromethane, and
1,2-dichloroethane, but any solvent compatible with the

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reaction conditions can be used. Reaction temperatures
in the 0° to 60°C range are suitable, with temperatures
near RT most convenient. The acyl thioimidate was
isolated by dilution of the reaction mixture with water

5   and filtration followed by air drying. This acyl
thioimidate was of sufficient purity to be used directly
in the following cyclization step.

The acyl thioimidate was cyclized to the 1,2,4-
triazole ring system by treatment with methylhydrazine.

10   The methylhydrazine could be added neat or as a solution
in a compatible solvent such as water. Any solvent
compatible with the reaction conditions can be used, with
toluene, 1,4-dioxane, THF, and short chain alcohols
preferred. The methylhydrazine can be added all at once

15   to the reaction mixture, or added in portions over a 1
hour time period. The cyclization can be carried out in
the temperature range of RT to reflux temperature of the
solvent being used. Ratios of the intermediate **3** to its
off-isomer **4** range from 6:1 to 40:1 depending upon the

20   reaction conditions used.
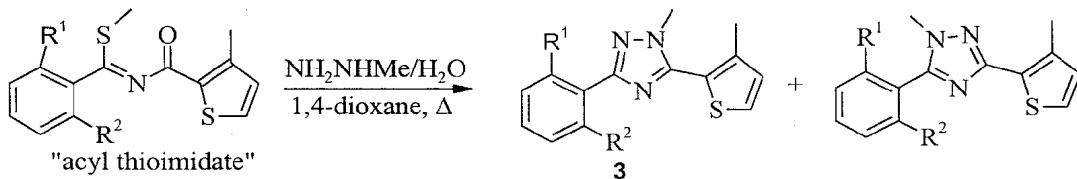
It was found most convenient to use 1,4-dioxane at a
cyclization temperature of 80°C to give a 30:1 ratio of
isomers. Workup consisted of removal of the solvent

25   followed by crystallization from a suitable solvent such
as 95% EtOH. Alternately, the reaction mixture could be
diluted with water and filtered to provide the
intermediate **3**. Air drying provided product of
sufficient purity for the next bromination step.

30   The last two steps illustrated in Scheme I are the
bromination of triazole **3** to give the dibromo

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intermediate **2**, followed by removal of one of the bromine atoms. Any standard brominating reagent known in the literature can be used, with Br_2 being the most convenient. Two to five molar equivalents of Br_2 can be used at temperatures from 25° to reflux temperature of the solvent. Time of reaction range from 1 hour to 24 hours. Any solvent compatible with bromination conditions can be used such as 1,4-dioxane, 1,2-dichloroethane, and acetic acid. The generated HBr can be neutralized by running the reaction in the presence of a proton acceptor such as sodium acetate. It was found most convenient to run the reaction in acetic acid with sodium acetate using four equivalents of Br_2.

The dibromo analogue **2** can be isolated or one may proceed directly into the next chemical transformation, if desired, without isolation. In the last step, zinc dust is added to the reaction mixture to reduce off the 5-bromine on the thiophene ring. Any known methods of aromatic halogen reduction could be used, but zinc dust was found most convenient. Two to three equivalents of zinc can be used; the extra molar equivalents were needed to reduce unreacted Br_2. The temperature of the reduction ranged from 25° to 90°C. This reduction is highly selective and leaves the 4-bromine of the thiophene ring unaffected. The product is conveniently isolated by dilution of the reaction mixture with water followed by filtration.

Another preferred synthetic method is illustrated in the following Scheme II:

Scheme II
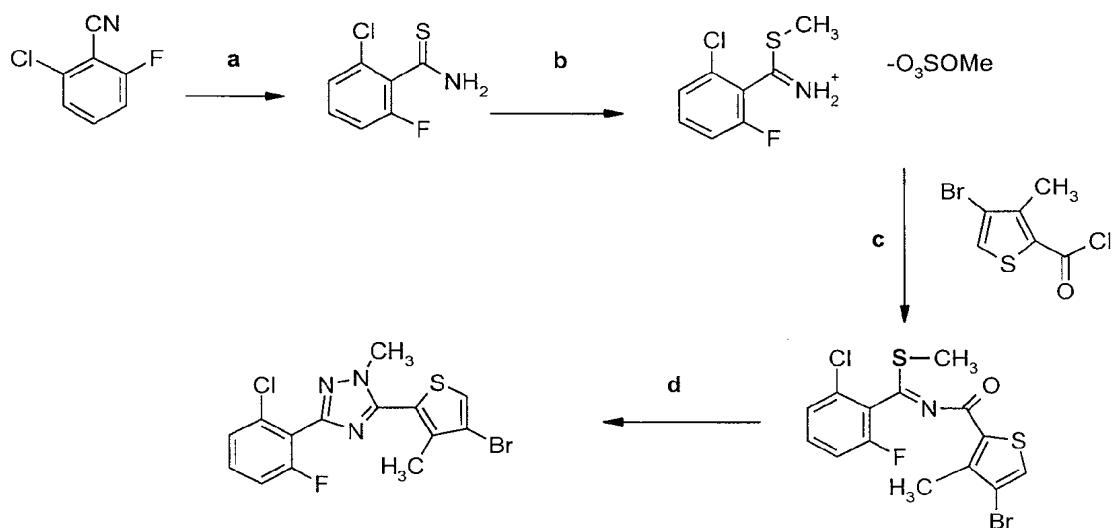
Conditions for each step in Scheme II are as follows: a)
H₂S/Et₃N/Pyridine, -20°C, b) (CH₃O)₂SO₂, 1,4-dioxane, 80°C,

5   c) pyridine, 4-bromo-TAC, 30°C,

d) MeNHNH₂/H₂O, 1,4-Dioxane, 80°C.

The 4-bromo-3-methyl-2-thiophenecarbonyl chloride
used in step **c** of Scheme I can be prepared using the
procedure illustrated in Scheme III:

10   Scheme III
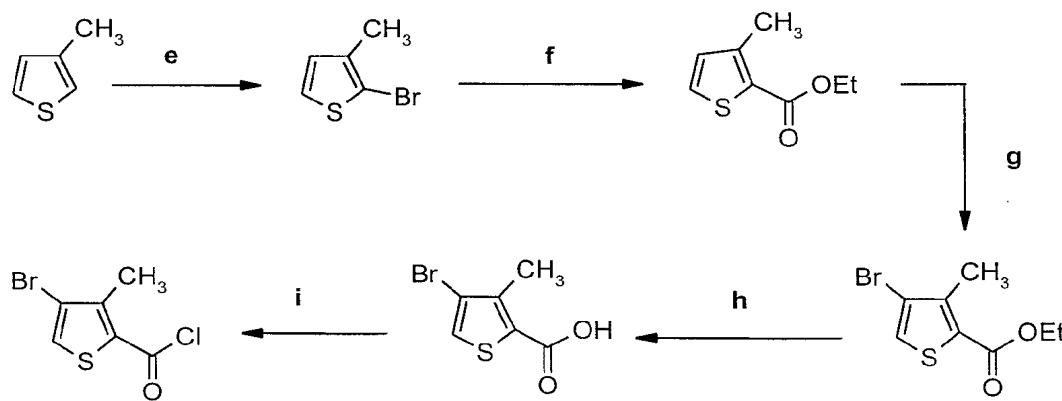
4-Bromo-TAC

Conditions for each step in Scheme III are as follows:
e) Br₂/succinimide, f) 10% Pd/C, DPPP, 0.2 mol %, CO

pressure, EtOH, NaOAc, g) i) 2 Br$_2$/2 NaOAc/HOAc, 80°C,
ii) Zn dust, HOAc/H$_2$O, h) NaOH/H$_2$O, i) SOCl$_2$/DMF, 1,2-DCE.

Scheme III illustrates use of ethyl 3-methyl-2-
thiophenecarboxylate as the intermediate utilized in step
5   **g,** but any short chain alkylester of 3-methyl-2-
thiophenecarboxylic acid may be used. These include, but
are not limited to, methyl, ethyl, propyl or butyl. Most
convenient are methyl or ethyl esters of 3-methyl-2-
thiophenecarboxylic acid.

10   One aspect of the invention is a novel preparation
of ethyl-3-methyl-2-thiophenecarboxylate via a palladium-
catalyzed carboxylation of 2-bromo-3-methylthiophene.

Methyl 3-methyl-2-thiophenecarboxylate may be
prepared by a Grignard reaction of 2-bromo-3-
15   methylthiophene with dimethylcarbonate. Either the
methyl or ethyl ester of 3-methyl-2-thiophene carboxylic
acid may be prepared by Fisher esterification with the
appropriate alcohol, or by reaction of 3-methyl-2-
thiophenecarboxylic acid chloride with the appropriate
20   alcohol.

Yet another preferred embodiment is illustrated in
Scheme IV:

Scheme IV
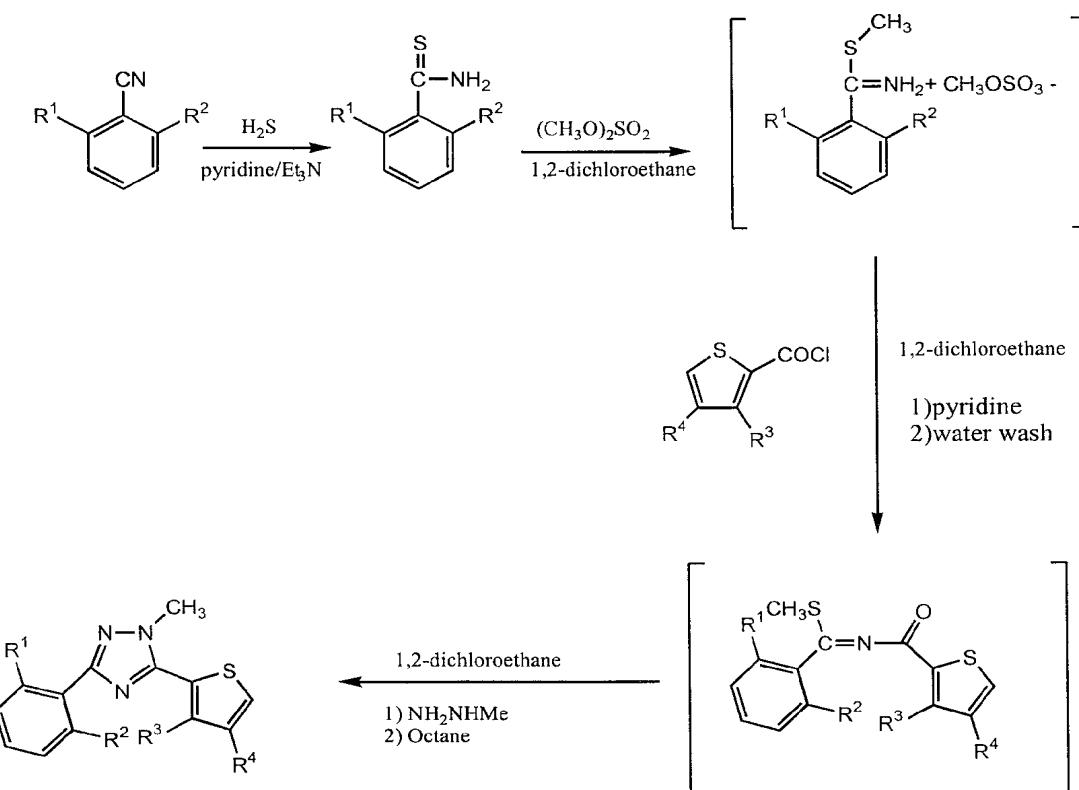
Noteworthy features of the embodiment illustrated in Scheme IV include:

1) the methyl sulfate salt of the benzthioimide is used;

2) 1,2-dichloroethane is used as the solvent in each step;

3) the synthesis is carried out in one pot, without isolation of intermediates;

4) octane is added in the final step to promote crystallization of the product.

The individual steps in the Scheme IV are described in detail hereafter:

The first step of this process involves the conversion of 2-chloro-6-fluorobenzonitrile to the thioamide. Any of the methods known in the chemical

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literature can be used for this thioamide formation
reaction. Sodium sulfide can be used as the sulfur
source, but it has been found most convenient to use
hydrogen sulfide gas. Reaction temperatures used are in
5   the -35° to 50° C range, with -10° to RT most convenient.
Any common solvent compatible with the reaction
conditions can be used. Pyridine and ethanol are
suitable. Any common amine base, for example
triethylamine, can be used.

10   The next three distinct chemical transformations are
most conveniently carried out in one process step,
without isolation of two intermediates. The two
intermediates can be isolated and characterized if
desired. In the first transformation, the 2-chloro-6-
15   fluorothiobenzamide is converted to the methyl
thioimidate. Any known imidate forming procedure known
in the literature can be used for this transformation.
Common methylating agents such as methyliodide,
methylbromide and dimethyl sulfate can be used. Any
20   common solvent compatible with the reaction conditions
can be used, with toluene, acetonitrile, THF, and 1,2-
dichloroethane most convenient. Reaction temperatures
range from RT to the reflux temperature of the solvent.
The thioimidate can be isolated as its salt or used
25   directly without isolation in the next transformation.

The thioimidate is next acylated with 3,4,5-
trichloro-2-thiophenecarbonyl chloride to give the
acylated adduct. This adduct can be isolated and
characterized if desired, but was found to be most
30   conveniently used directly without isolation. Any known
acylation conditions can be used for this transformation.
Any common organic and inorganic base can be used, with
Na_2CO_3, $NaHCO_3$, pyridine and triethylamine most
convenient. Solvents preferred include THF,
35   dichloromethane, and 1,2-dichloroethane, but any solvent

compatible with the reaction conditions can be used. Reaction temperatures in the 0° to 60° C range are suitable, with temperatures near RT most convenient.

5   The acylated adduct is finally cyclized to the 1,2,4-triazole ring system by treatment with methylhydrazine. A two step procedure using hydrazine to give the unsubstituted triazole followed by methylation could be used, but it is convenient to use methylhydrazine directly. The methylhydrazine can be

10   added neat or as a solution in a compatible solvent such as water. Any solvent compatible with the reaction conditions can be used, with toluene, THF, and 1,2-dichloroethane preferred. The methylhydrazine can be added all at once to the reaction mixture, or added in

15   portions over a 1 hour time period. The cyclization can be carried out in the temperature range of RT to reflux temperature of the solvent being used. Ratios of the desired product to its off-isomer range from 1:4 to 50:1 depending upon the reaction conditions used. It is most

20   convenient to use 1,2-dichloroethane at a cyclization temperature of 70° C to give a 38:1 ratio of 1-methyl-3-(2-chloro-6-fluoro)phenyl-5-(3,4,5-trichloro-2-thienyl)-1H-1,2,4-triazole to its "off isomer."

Example 4

25   This example illustrates the process of Scheme IV.

A.   Preparation of 2-chloro-6-fluorobenzthioamide in pyridine/triethylamine solvent.

2-Chloro-6-fluorobenzonitrile, (99.1%, 62.2 g, 0.40 mol) was weighed into a 1-L three-necked roundbottom

30   flask equipped with a condenser and an overhead electric stirrer, along with Et_3N (78 mL, 56.6 g, 0.56 mol) and 180 mL (176.04 g, 2.23 mol) of pyridine. The reactor was purged with a slow stream of N_2 and vented to a 13% bleach solution. The stirring solution was cooled to -19°C in a

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CCl_4/dry ice bath, and H_2S gas (33.6 g, 0.99 mol) was
sparged below the liquid surface at a rate of 0.4 g/min
over a period of 82 min. During the gas addition, the
solution temperature rose to -11°C. The yellow-green
5   solution was allowed to gradually warm to 25°C and stir
overnight with a slow N_2 purge of the reactor head space
into bleach solution. The solution was poured into 1.6 L
of ice water, stirred, and the resulting white crystals
were collected on a buchner funnel and rinsed with
10   additional water. After 2 h of air drying, the moist
filter cake was vacuum oven dried for 5 h at 65°C to give
54.5 g of 2-Chloro-6-Fluorobenzthioamide (72% wt. %
yield), mp 155-160°C, having a GC area % purity of 98.8 %
and containing 1.2 % 2-Chloro-6-fluorobenzonitrile.

15   B. Preparation of 2-chloro-6-fluorobenzthioamide in
ethanol/triethylamine solvent.

2-Chloro-6-fluorobenzonitrile, (99.1%, 15.2 g, 0.10 mol)
was weighed into a 1-L three-necked roundbottom flask
equipped with a condenser and an overhead electric
20   stirrer, along with Et_3N (41 mL, 29.8 g, 0.29 mol) and 54
mL of 95% ethanol. The solution was cooled to 0°C with
an ice bath and H_2S gas (13.5 g, 0.40 mol) was sparged
below the liquid surface at a rate of 0.2 g/min over a
period of 70 min. The ice bath cooling was continued for
25   2 h, then the flask was allowed to gradually warm to room
temperature. The yellow solution was poured into 426 g
of stirring ice water in a 1 L Erlenmeyer flask, and the
resulting white solid was collected on a buchner funnel
and rinsed with additional water. This filter cake was
30   dissolved in 1,2-dichloroethane and evaporated to dryness
on a rotary evaporator (67°C bath) to ensure dryness,
giving 13.42 g (72 % weight % yield) of the thioamide as
a white solid.

C. 3,4,5-Trichloro-2-thiophenecarbonyl chloride

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A mixture of 20.4 g (0.088 mole) of 3,4,5-trichloro-2-
thiophenecarboxylic acid, 7.3 mL (0.1 mole) of thionyl
chloride, 0.2 mL of DMF and 80 mL of 1,2-dichloroethane
was heated at reflux temperature for 3 h. The reaction
5   mixture became a clear solution after 1 h of heating.
The mixture was allowed to cool to RT, concentrated *in
vacuo* and exposed to high vacuum to give 22.0 g (>98 %
wt) an oil which solidified upon standing to an off-white
powder, mp 37°-41° C.

10 D. 1-Methyl-3-(2-chloro-6-fluorophenyl)-5-(3,4,5-
trichloro-2-thienyl)-1H-1,2,4-triazole

    A mixture of 94.82 g (0.5 mole) of 2-chloro-6-
fluorobenzthioamide, 50 mL (0.525 mole) of dimethyl
sulfate, and 800 mL of 1,2-dichloroethane was heated at
15 reflux temperature for 1 h. LC analysis indicated
complete conversion to the thioimidate. The reaction
solution was cooled to RT with ice-bath cooling, and the
thioimidate salt precipitated from the solution. To the
thick slurry was added 100 mL (1.25 mole) of pyridine.
20 The salts instantly dissolved into solution, followed by
immediate precipitation of pyridine salts. After further
cooling to 10° C, 125 g (0.5 mole) of 3,4,5-trichloro-2-
thiophenecarbonyl chloride dissolved in 200 mL of 1,2-
dichloroethane was added in three portions. Temperature
25 of the reaction mixture rose to 20° C during each
addition and was allowed to cool back to 10° C before the
next addition. The reaction mixture was allowed to stir
at RT for 0.5 h. LC analysis indicated major acylated
thioimidate and <2% area of starting thioimidate. To the
30 slurry was added 1.0 L of water and the layers separated.
LC internal standard analysis of the organics indicated a
94% in-pot yield of the acylated intermediate. The 1,2-
dichloroethane solution was heated to 70° C, and a
solution of 40 mL (0.75 mole) of methylhydrazine in 60 mL
35 of water was added via a pump over 20 min. The

temperature of the reaction mixture was maintained
between 70° and 73° C. The solution was heated an
additional 2 h, when GC analysis indicate no remaining
acylated intermediate and a 38:1 ratio of desired
5   product/off-isomer. The reaction mixture was cooled to
RT, and 500 mL of octane followed by 1 L of 0.5 N LiOH
was added. After stirring for 10 min, the layers were
separated. The organic solution was then stirred with
750 mL of a 2% bleach solution for 0.25 h to remove
10   remaining mercaptan compounds. The temperature of the
mixture rose to 31° C during this reaction. The layers
were separated and upon concentration of the 1,2-
dichloroethane on a roto-evaporator, a tan sandy
precipitate formed. This solid was filtered and exposed
15   to vacuum oven drying at 40° C to give 144.8 g (73% wt)
of the desired product as a tan crystalline powder. GC
analysis indicated <0.2% area of the off-isomer, and LC
internal standard analysis indicated a 98% purity, giving
an overall isolated 72% yield of 1-methyl-3-(2-chloro-6-
20   fluoro)phenyl-5-(3,4,5-trichloro-2-thienyl)-1H-1,2,4-
triazole.

<u>Example 5</u>
<u>3-(2-Chloro-6-fluorophenyl)-1-methyl-5-(3-methyl-4-bromo-
2-thienyl)-1H-1,2,4-triazole</u>
25   This example illustrates the process of Scheme I.

A. 2-Chloro-6-fluorobenzenecarbothioamide

2-Chloro-6-fluorobenzonitrile (1230 g, 7.91 mol) was
weighed into a 22 L jacketed glass reactor (without
bottom drain), along with Et_3N (1.5 L, 10.76 mol) and
30   pyridine (2.4 L, 29.67 mol) and the stirring solution was
cooled to -18°C under a blanket of N_2. The reactor N_2
purge mineral oil bubbler was vented to a carboy
containing 16 L of 12% bleach solution. Hydrogen sulfide
gas (407 g, 11.94 mol) was introduced below the surface
35   of the cold reactor solution over a period of 5.5 hrs.

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During this time the reactor temperature rose from -18 to -4°C. The solution was stirred overnight at -7°C (16 hrs), sampled by GC to ensure complete conversion of 2,6-CFBN, then quenched by vacuum transfer of the reactor

5 solution into a second 22 L flask containing 14 L of cold water stirring at 300 RPM (Note: Quenching into a well-stirred tank of cold water produces small white particles of easily filtered product). After the vacuum transfer was completed, another 2 L of cold water was added to the

10 stirring slurry. The light yellow slurry of white solid was drained from the quench tank into bottles, and the solid product was collected by filtration through a course glass buchner funnel, followed by washing of the solid product with an excess of de ionized water. The

15 white solid was air suction dried for 3 h, air dried in a glass pan overnight, then dried in a vacuum oven at 50°C at 0.3 mm Hg for 8 hrs to give 1004 g (67%) of dry 2-chloro-6-fluorobenzenecarbothioamide, m.p. 153-157°C.

B. Methyl 2-chloro-6 fluoro-N-[(3-methyl-2-
20 thiophene)carbonyl]benzenecarboximidothioate
To a 22 L jacketed glass reactor under a N₂ purge was added 6 L of 1,4-dioxane via a pump. After the mechanical stirrer had been started, 1140 g (6.0 mol) of 2-chloro-6 fluorobenzenecarbothioamide was added to the

25 reactor, followed by 630 mL (6.65 mol) of dimethyl sulfate. The reaction mixture was heated to 80°C for 1.5 h. During the course of heating, the reaction mixture became a solution near 55°C, with a precipitate reforming as the reaction proceeded. LC analysis indicated <2%

30 area starting thioamide and 96% area methyl 2-chloro-6-fluorobenzenecarboximidothioate methylsulfonate salt ("thioimidate"). The reaction mixture was cooled to 30°C, and 1.2 L (15 mol) of pyridine was added. When the reaction temperature had fallen back below 30°C, 970 g

35 (6.04 mole) of 3-methyl-2-thiophenecarbonyl chloride

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("acid chloride") was added via a PE dropping funnel over
20 min. An exotherm of seven degrees was observed during
this addition. After stirring at room temperature for 1
h, LC analysis indicated < 3% area of the thioimidate and
5   93% area acyl thioimidate. To the reaction mixture was
added 9 L of water, and the mixture stirred at room
temperature for 1 h. The mixture was filtered through a
crock filter with vacuum removal of the mother liquor
into a second 22 L glass reactor. The white solid was
10 air dried in a glass pan overnight to give 2000 g of a
white powder, 98% LC area. This material was used
directly in the next step without further purification.

C. 3-(2-Chloro-6-fluorophenyl)-1-methyl-5-(3-methyl-2-
15 thienyl)-1H-1,2,4-triazole
To a 22 L jacketed glass reactor under a N₂ purge was
added 9 L of 1,4-dioxane via a pump. The N₂ purge outlet
was connected to a carboy containing 12 L of fresh 12% wt
bleach solution. To the stirred dioxane was added 1970 g
20 (6 mol) of methyl 2-chloro-6 fluoro-N-[(3-methyl-2-
thiophene)carbonyl]benzenecarboximido-thioate and the
mixture heated to 80°C. During heating the mixture became
a clear solution. Upon reaching 80°C, a solution of 400
mL (7.5 mol) of methylhydrazine in 600 mL of water was
25 added over 20 min via a pump. The mixture was heated
near 80°C for 3.5 h, when GC area analysis indicated 2%
starting acyl thioimidate, 94% desired product, and 3%
off-isomer **4**. The reaction mixture was cooled to 30°C and
vacuum transferred to a roto-evaporator connected to
30 bleach trapping. The reaction mixture was concentrated
to an amber oil, dissolved in 800 mL of 95% EtOH, and
transferred to a 4 L Erlynmeyer flask. The solution was
scratched and seeded with the title compound and allowed
to crystallize in a refrigerator overnight. After
35 filtration the precipitate was air dried in a glass pan

overnight to give 1376 g of an off-white powder, 99% area
GC. This material was used directly in the next step
without further purification.

D. 3-(2-Chloro-6-fluorophenyl)-1-methyl-5-(3-methyl-4-
5 bromo-2-thienyl)-1H-1,2,4-triazole

The triazole 3-(2-Chloro-6-fluorophenyl)-1-methyl-5-
(3-methyl-2-thienyl)-1H-1,2,4-triazole (1715 g, 5.57 mol)
and anhydrous sodium acetate (1830 g, 22.3 mol) were
weighed as solids into a 22 L jacketed glass reactor
10 under a slow N_2 purge, followed by 8.5 L glacial AcOH.
Heating of the mixture was begun, and at 66°C a solution
of Br_2 (1.15 L, 22.3 mol) in 2.5 L glacial AcOH was added
by peristaltic pump over a period of 40 min., at a rate
to keep the reaction temperature below 85°C. During heat
15 up most of the solids dissolve. The stirring red
solution was heated 1 h at 80°C and then a sample was
removed and analyzed by GC to verify >99% conversion to
the dibromo intermediate. Cooling was placed on the
jacket, and 1695 g ice was added to the solution, which
20 dropped the temperature from 70°C to 50°C. At 38°C zinc
powder (815 g, 12.5 mol) was added in 55 g shots over a
period of 40 min to dispel excess Br_2. During this
addition the reactor temperature rose to 71°C.
Additional zinc powder (650 g, 9.9 mol) was then added in
25 50 g shots over a period of 50 min with a stream of N_2
passing through the reactor to dispel H_2 gas safely.
During the addition of this second portion of zinc
powder, jacket heating (85°C) was applied to bring the
reaction mixture to 78°C (Note: zinc addition at this
30 point leads to H_2 gas evolution and should be done at such
a rate as to control the rate of evolution and maintain
precautions against flammability and explosion hazards).
After zinc addition was completed, the reactor was
stirred at 78°C for 15 min, then was sampled for GC
35 analysis (Note: the reactor can be maintained at this

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point at 80°C overnight to keep the product dissolved if
insufficient time exists to carry out the filtration).
The solution was filtered warm through a layer of celite
on a course glass buchner funnel (pre warmed at 100°C) to
5   remove residual zinc particulates. The celite cake was
washed with a small amount of additional glacial AcOH.
The clear light yellow filtrate was diluted with cold
water while stirring until the cloud point was reached
and product crystallization began. Excess cold water was
10   then added to precipitate the remainder of the solid
product. Part of this dilution was done in 4 L
Erlenmeyer flasks with magnetic stirring and part was
done in a second 22 L reactor. Approximately eight 2 L
portions of solution were filtered from the reactor, and
15   approximately 18 L of quench water was used. The white
solid product was collected on course glass buchner
funnels, rinsed with additional de-ionized water, air
suction dried for a few hours, then transferred to glass
trays and air dried overnight. A final vacuum oven
20   drying for 2.5 hrs at 0.3 mm Hg and 30°C was carried out
to give 2236 g of 3-(2-Chloro-6-fluorophenyl)-1-methyl-5-
(3-methyl-4-bromo-2-thienyl)-1H-1,2,4-triazole as a white
solid (theory = 2154 g), mp 118-120°C. A GC area %
analysis indicated a purity of 98.1%.

25   Example 6

        4-Bromo-3-methyl-2-thiophenecarbonyl chloride

This example illustrates the process of Scheme III.

A. Ethyl 3-methyl-2-thiophenecarboxylate via palladium
catalyzed carbonylation of 2-bromo-3-methylthiophene
30   (Scheme III, step **f**)

        2-Bromo-3-methylthiophene (Lancaster, 26.4 g, 0.149
mol), Pd(OAc)$_2$ (0.213 g, 0.95 mmol), 1,3-
bis(diphenylphosphino) propane (0.49 g, 1.2 mmol), Na$_2$CO$_3$
(21.1 g, 0.20 mol), and 200 mL abs EtOH were placed into

a 450 mL Hastalloy-C stirred pressure reactor, purged
with N_2, then pressurized with 490 psig CO, and the
stirring reactor was heated to 120°C for 36 hrs. Analysis
of the reaction mixture by gas chromatography showed 1.3
5   % and 96.9 % area % starting bromomethylthiophene and
carbonylation product, respectively. After cooling and
venting, the reactor contents were filtered and
evaporated to give a light yellow oil/solid mixture.
This residue was extracted with 1,2-dichloroethane and
10   water, and the organic phase was evaporated to give an
oil. Filtration of this oil to remove residual salt gave
20.7 g (81% wt. % yield) of orange oil as ethyl 3-methyl-
2-thiophenecarboxylate. ^{13}C NMR {^{1}H} CDCl$_3$: δ 162.8,
145.9, 131.7, 129.9, 127.0, 60.6, 15.9, 14.4 ppm.

15   B. Ethyl 4-bromo-3-methyl-2-thiophenecarboxylate (Scheme
III, step **g**)

A solution of ethyl 3-methyl-2-thiophenecarboxylate
(20.0 g, 0.118 mol) and sodium hydroxide (12.3 g, 0.307
mol) in acetic acid (75 mL) was heated to 60 °C. Bromine
20   (46.9 g, 0.294 mol) was added dropwise at such a rate so
as to maintain the temperature of the reaction mixture at
<85 °C. When the addition was complete, the resulting
solution was stirred at 85 °C for 6 hours, at which time
analysis by gas chromatography/mass spectrometry showed
25   complete conversion to ethyl 4,5-dibromo-3-methyl-2-
thophenecarboxylate. The solution was allowed to cool to
50 °C and zinc dust (15.4 g, 0.236 mol) was added in 3
gram portions such that the exotherm was controlled to
remain below 85 °C. When the addition was completed, the
30   resulting slurry was stirred at 85 °C for one hour. The
solution was filtered hot through a small bed of celite.
Water (300 mL) was added and the mixture was extracted
with heptanes (300 mL). The organic phase was washed
with water, then concetrated to dryness to give 26.9 g
35   (89%) as an off white oil which slowly crystallized upon

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standing at ambient temperature. In a similar fashion,
methyl 3-methyl-2-thiophenecarboxylate may be converted
methyl-4bromo-3-methyl-2-thiophenecarboxyltate in 97%
yield.

5   C. 4-Bromo-3-methyl-2-thiophenecarboxylic acid
(Scheme III, step **h**)

To a solution of ethyl 4-bromo-3-methyl-2-
thiophenecarboxylate (5.0 g, 0.0201 mol) in THF/MeOH/H_2O
(4:1:1, v/v/v, 50 mL) was added NaOH (1.00 g, 0.0251 mol)

10   and the resulting mixture was stirred at ambient
temperature overnight. The mixture was acidified by
adding 6 N HCl (100 mL) and water (100 mL). The
resulting fine white precipitate was filtered off, washed
with water and dried to give 3.80 g (86%) of 4-bromo-3-

15   methyl-2-thiophenecarboxylic acid as a fine white solid,
mp 188-189°C.

D. 4-Bromo-3-methyl-2-thiophenecarbonyl chloride (Scheme
III, step **i**)

          A slurry of 1.11 g (5 mmole) of 4-bromo-3-methyl-2-

20   thiophenecarboxylic acid, 0.44 mL (6 mmole) of thionyl
chloride, 5 drops of DMF, and 10 mL of 1,2-dichloroethane
was heated at 80° C for 1.5 h. The clear solution was
cooled and concentrated on a roto-evaporator. The
residue was dissolved in 5 mL of 1,2-dichloroethane and

25   reconcentrated on a roto-evaporator to give 1.2 g of a
tan solid, 97 % pure (GC area). This acid chloride was
used without further purification.

<u>Example 7</u>

<u>3-(2-Chloro-6-fluorophenyl)-1-methyl-5-(4-bromo-3-methyl-</u>

30   <u>2-thienyl)-1H-1,2,4-triazole</u>

This example illustrates the process of Scheme II.

A. Methyl 2-chloro-6-fluoro-N-[(4-bromo-3-methyl-2-
thiophene)carbonyl]benzenecarboximidothioate (Scheme II,
step **c**)

A mixture of 0.95 g (5 mmole) of 2-chloro-6-
fluorobenzenecarbothioamide, 0.5 mL (5.5 mmole) of
dimethyl sulfate, and 10 mL of 1,4-dioxane was heated at
80° C for 1 h. The clear solution was allowed to cool to
5   room temperature, where a white precipitate formed. To
the slurry was added 1.0 mL (12.5 mmole) of pyridine,
followed by 1.2 g (5 mmole) of 4-bromo-3-methyl-2-
thiophenecarbonyl chloride. The reaction mixture turned
brown in color and a gummy insoluble material formed
10   which made stirring difficult. The mixture was heated at
50° C for 1.5 h. The mixture was poured onto ice and a
gummy solid formed which solidified upon stirring.
Stirring was continued for 1 h, and the mixture was
filtered to give 1.74 g (85% wt) of a tan powder, mp
15   106°-109°. This material was used without further
purification.

B.   3-(2-Chloro-6-fluorophenyl)-1-methyl-5-(4-bromo-3-
methyl-2-thienyl)-1H-1,2,4-triazole (Scheme II, step **d**)

A mixture of 1.22 g (3 mmole) of methyl 2-chloro-6-
20   fluoro-N-[(4-bromo-3-methyl-2-thiophene)carbonyl]-
benzenecarboximidothioate in 5 mL of 1,4-dioxane was
heated to 75° C. To the solution was added in one
portion 0.24 mL (4.5 mmole) of methylhydrazine in 0.5 mL
of water. After heating here for 1.5 h, the solution was
25   cooled and poured onto ice. The initially formed gummy
solid was stirred for 1 h and filtered to give 1.03 g
(89% wt) of an off-white powder. GC analysis indicated
96.4/1.7 area ratio of the desired product to off-isomer.

<u>Claims</u>

1.   A process for preparing a compound of the
formula (1)
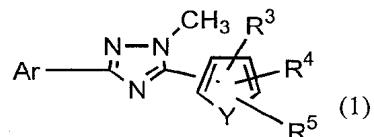
$$\text{Ar} \overset{\displaystyle N-N-CH_3}{\underset{\displaystyle N}{\diagdown\!\!\!\diagup}}\!\!\overset{R^3}{\underset{Y}{\diagup\!\!\!\diagdown}}\!\!\overset{R^4}{\underset{R^5}{\diagup}} \quad (1)$$

5   wherein

Ar is substituted phenyl;

Y is O or S;

R^3 is selected from H, halo, lower alkyl, (C_7-C_{21})
straight or branched chain alkyl, hydroxy, lower alkoxy,
10   haloalkyl, haloalkoxy, alkoxyalkyl, alkoxyalkoxy, lower
alkenyl, lower alkynyl, haloalkenyl, CN, NO_2, COR^6, CO_2R^6,
$CON(R^6)_2$, (C_3-C_6) cycloalkyl, $S(O)_mR^6$, $-OSO_2R^6$, SCN, $-$
$(CH_2)_nR^6$, $-CH=CHR^6$, $-C\equiv CR^6$, $-(CH_2)_qOR^6$, $-(CH_2)_qSR^6$, $-$
$(CH_2)_qNR^6R^6$, $-O(CH_2)_qR^6$, $-S(CH_2)_qR^6$, $-NR^6(CH_2)_qR^6$,

15   $\overset{\displaystyle\longrightarrow}{N}\underset{\displaystyle\smile}{(CH_2)_p}$, $\overset{\displaystyle\longrightarrow}{N}\underset{\displaystyle\smile}{O}$, $-NR^6\overset{O}{\overset{\|}{C}}R^6$, $-NR^6\overset{O}{\overset{\|}{C}}OR^6$,
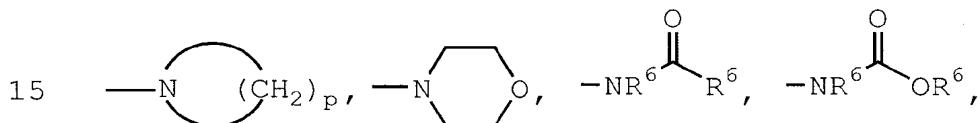
$-NR^6\overset{O}{\overset{\|}{C}}N(R^6)$, $\overset{N-OR^6}{\overset{\|}{C}}R^6$, $-O\overset{O}{\overset{\|}{C}}R^6$, or $-S\overset{O}{\overset{\|}{C}}R^6$, pyridyl,
substituted pyridyl, isoxazolyl, substituted isoxazolyl,
naphthyl, substituted naphthyl, phenyl, substituted
phenyl, thienyl, substituted thienyl, pyrimidyl,
20   substituted pyrimidyl, pyrazolyl, or substituted
pyrazolyl;

R^4 and R^5 are independently H, halo, lower alkyl,
lower alkoxy, haloalkyl, haloalkoxy, CN, CO_2R^6, $CON(R^6)_2$,
or $S(O)_m$ alkyl, or

if R^4 and R^5 are attached to adjacent carbon atoms, they may join to form a 5 or 6 member saturated or unsaturated carbocyclic ring which may be substituted by 1 or 2 halo, lower alkyl, lower alkoxy or haloalkyl

5   groups;

    R^6 is H, lower alkyl, haloalkyl, lower alkenyl, lower alkynyl, phenyl, or substituted phenyl;

    m is 0, 1, or 2;

    n is 1 or 2;

10   p is an integer from 2 to 6; and

    q is 0 or 1;

which comprises the steps of:

    (a)   reacting a compound of formula (2)

$$\text{Ar}\!-\!\overset{\displaystyle S-R^7}{\underset{\displaystyle NH}{\diagup\!\!\!\diagdown}}\qquad (2)$$
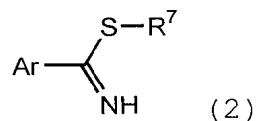
15   wherein Ar is as defined above and R^7 is lower alkyl, or an acid addition salt thereof, with an acid chloride of the formula (3)

$$\text{Cl}\!-\!\overset{\displaystyle O}{\underset{}{\overset{\displaystyle \|}{C}}}\!\diagdown\!\!\diagup^{R^3}_{R^4}\!\!\diagdown_Y\!\!\diagdown_{R^5}\qquad (3)$$
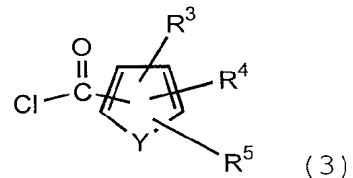
wherein Y, R^3, R^4, and R^5 are as defined in formula (1),

20   in an inert organic solvent the presence of an organic or inorganic base to produce an adduct-intermediate of formula (4)

$$\text{Ar}\!-\!\overset{\displaystyle S^{\diagup R^7}}{\underset{\displaystyle N}{\diagup\!\!\!\diagdown}}\!-\!\overset{\displaystyle O}{\underset{}{\overset{\displaystyle \|}{C}}}\!\diagdown\!\!\diagup^{R^3}_{R^4}\!\!\diagdown_Y\!\!\diagdown_{R^5}\qquad (4)$$
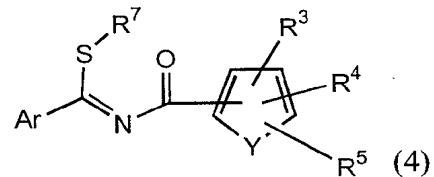
wherein Ar, Y, R^3, R^4, and R^5 are as defined above and R^7 is lower alkyl; and

(b) with or without prior isolation of the adduct-intermediate of formula (4), reacting said adduct-intermediate with methyl hydrazine to produce the compound of formula (1).

2. A process of claim 1 wherein an acid addition salt of the reactant of formula (2) is used.

3. A process of claim 2 wherein the acid addition salt of the reactant of formula (2) is the hydroiodide or the methyl sulfate salt.

4. A process of claim 1 wherein a compound of formula (2a)
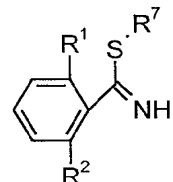
wherein R^1 and R^2 are independently F or Cl, and

R^7 is lower alkyl, or an acid addition salt thereof, is reacted with an acid chloride of the formula (3a)

(3a)
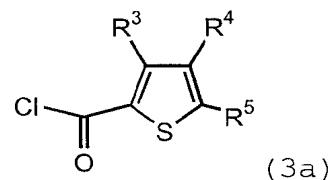
wherein R^3, R^4 and R^5 are independently H, CH$_3$, Cl, or Br to produce the adduct-intermediate of formula (4b)

(4b)
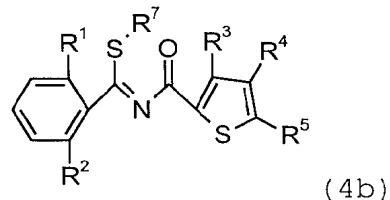
wherein R^1, R^2, R^3, R^4, R^5, and R^7 are as defined above, and, with or without isolation of said adduct-intermediate of formula (4b), said adduct-intermediate is reacted with methyl hydrazine to produce the compound of formula (1b)

(1b)
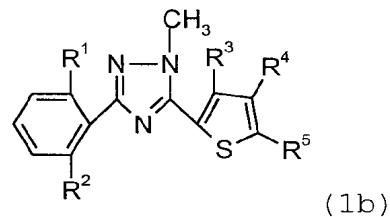
wherein R^1, R^2, R^3, R^4, and R^5 are as defined above.

5.   A process of claim 4 wherein R^3 and R^7 are CH_3, and R^4 and R^5 are both H or both Br, or R^4 is Br and R^5 is H.

6.   A process of claim 5 wherein R^1 is F, R^2 is Cl, R^4 is Br, and R^5 is H or Br.

7.   A process of claim 6 wherein

R^5 is Br, and

the product of formula
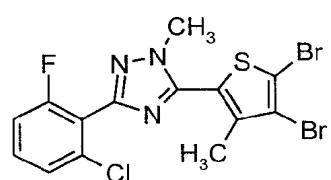
is reacted with zinc dust to provide a compound of formula
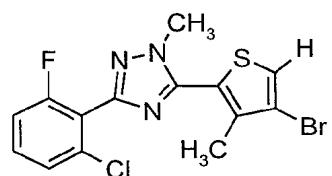
8.   A process of any one of claims 1 to 7 wherein the adduct intermediate is reacted with methyl hydrazine in 1,4-dioxane.

9.   A compound of the formula

wherein

Ar is substituted phenyl,

Y is O or S,

R^3 is selected from H, halo, lower alkyl, (C_7-C_{21}) straight or branched chain alkyl, hydroxy, lower alkoxy, haloalkyl, haloalkoxy, alkoxyalkyl, alkoxyalkoxy, lower alkenyl, lower alkynyl, haloalkenyl, CN, NO_2, COR^6, CO_2R^6, $CON(R^6)_2$, (C_3-C_6) cycloalkyl, $S(O)_mR^6$, $-OSO_2R^6$, SCN, $-(CH_2)_nR^6$, $-CH=CHR^6$, $-C\equiv CR^6$, $-(CH_2)_qOR^6$, $-(CH_2)_qSR^6$, $-(CH_2)_qNR^6R^6$, $-O(CH_2)_qR^6$, $-S(CH_2)_qR^6$, $-NR^6(CH_2)_qR^6$,

substituted pyridyl, isoxazolyl, substituted isoxazolyl, naphthyl, substituted naphthyl, phenyl, substituted phenyl, thienyl, substituted thienyl, pyrimidyl, substituted pyrimidyl, pyrazolyl, or substituted pyrazolyl;

R^4 and R^5 are independently H, halo, lower alkyl, lower alkoxy, haloalkyl, haloalkoxy, CN, CO_2R^6, $CON(R^6)_2$, or $S(O)_m$ alkyl, or

if R^4 and R^5 are attached to adjacent carbon atoms, they may join to form a 5 or 6 member saturated or unsaturated carbocyclic ring which may be substituted by 1 or 2 halo, lower alkyl, lower alkoxy or haloalkyl groups;

R^6 is H, lower alkyl, haloalkyl, lower alkenyl, lower alkynyl, phenyl, or substituted phenyl;

m is 0, 1, or 2;

n is 1 or 2;

p is an integer from 2 to 6;

q is 0 or 1; and

R^7 is lower alkyl.

10. A compound of claim 9 having the formula (4a)
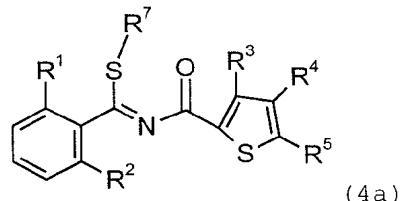
(4a)

wherein

R^1 and R^2 are independently F or Cl;

R^3, R^4, and R^5 are independently H, CH_3, Cl or Br; and

R^7 is lower alkyl.

11. A compound of claim 10 wherein

R^7 is methyl, R^1 is F, R^2 is Cl, and

(a) R^3, R^4, and R^5 are each Cl;

(b) R^3 and R^4 are each Br and R^5 is H; or

(c) R^3 is CH_3, R^4 is Cl or Br, and R^5 is H.

12. The methyl sulfate salt of the compound of the formula
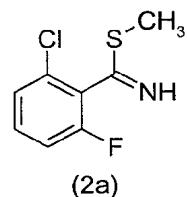
(2a)

INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 7   C07D409/04   C07D405/04   C07D333/38   C07D307/68   C07C327/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7   C07D   C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	BE 786 562 A (GRUPPO LEPITATIT S.P.A.) 16 November 1972 (1972-11-16) page 2, line 29 -page 3, line 20; claims	1-12
A	T.W. STROHMEYER ET. AL.: "New Synthesis of 2,4-Dialkyl(or diaryl) pyrazolo'1,5-a! 1,3,5-triazines." JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 22, no. 1, January 1985 (1985-01), pages 7-10, XP000881466 page 8; table 1	9-12

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[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 March 2000	23/03/2000

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INTERNATIONAL SEARCH REPORT

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	M. A. PEREZ ET. AL. : "Regioselective Synthesis of 1,2,4-Triazole and 1,2,4-Oxadiazole Derivatives." SYNTHESIS, vol. 1983, no. 6, June 1983 (1983-06), pages 483-6, XP002132293 cited in the application whole article	1-12
P,A	WO 98 47894 A (DOW AGROSCIENCES LLC) 29 October 1998 (1998-10-29) claims; examples	1-12

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

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